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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,104	09/27/2000	Alan P. Kozikowski	ZAA-012.01	6012

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EXAMINER	
HUANG, EVELYN MEI	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,104	KOZIKOWSKI ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 27-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 27-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18, 27-44 are pending. Claims 19-26, 45-59 have been canceled according to the amendment filed on 2-5-2003.

Claim Rejections - 35 USC § 112(2)

2. The rejection for Claims 1-18, 27-44 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment and applicant's remarks.

Claim Rejections - 35 USC § 112(1)

3. The rejection for Claims 1-18, 27-44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record since R15, R16, Q1 and Q2 as defined are not described in the specification.

Applicants maintains that these terms are introduced in response to the previous Office Action, issued September 9, 2002 to address a 35 U.S.C. 112 second paragraph rejection made by the Examiner. Applicants replaced the art-recognized terms, acyl, ether, sulfonyl, carbonyl, phosphoryl, amido, ester, etc, with structural formulae that explicitly show the point of attachment. Doing so required the introduction of terms R15, R16, Q1 and Q2. Applicants stress that support for such terms comes from taking them together to define the various originally disclosed terms acyl, ether, sulfonyl, carbonyl, phosphoryl, amido, and ester, rather than considering them individually.

Applicant further submit that if the Examiner maintains this written description rejection, then they should be able re-replace the structural formulas with the originally disclosed terms acyl, ether, sulfonyl, carbonyl, phosphoryl, amido, and ester because such terms are understood by one of ordinary skill in the art to be monovalent in the context of formula 1.

On the contrary, acyl, ether, sulfonyl, carbonyl, phosphoryl, amido, and ester etc is known in the art as bivalent groups. While it is clear that they are attached to the tropane core, it

is clear that there is a requirement for an additional group to be attached thereto. The fact that new terms R15, R16, Q1 and Q2 have to be introduced to the structural formulae points to the incomplete description for these groups as recited.

Claim Rejections - 35 USC § 112(1)

4. The 112 first paragraph rejection set forth in the office action mailed on 9-9-2002 is maintained for claims 1-4, 7-18, 27-30, 33-44 for reasons of record.

Applicant has submitted references, Exhibits A-D, to show that certain tropane compounds were available at the time of the filing of the application, and the combined references show a total of 15 substituents on the tropane ring.

However, these references show 2, or at the most 4 substituents on the tropane ring at one time, which is quite different from the '15 substituents' or the instant 14 substituents on the tropane ring at the same time, each of which may be optionally substituted aryl, heteroaryl, cylcoalkyl, polycyclic, heterocyclic etc. , wherein 'substituted' is 'contemplated to include all permissible substituents of organic compounds.....the invention is not intended to be limited in any manner by the permissible substituents of organic compounds' (page 9 of the specification, lines 16-25).

The instant claims are drawn to a highly substituted tropane compounds. The preparation of the 8 example compounds, however, is limited to A being a double bond, R1 is phenyl, substituted phenyl, naphthyl or furyl, R_2 to R_{13} are hydrogen, R14 is a carboxylate (Fig. 3), the scope of the claims therefore does not commensurate with that of the objective enablement. Undue experimentation would be required for the skill in the art to make these highly substituted compounds, (where the ring substituents are further substituted by bulky substituents), especially when the starting materials have not been disclosed.

Applicant maintains that the Examiner has not satisfy the burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility.

The issue here is not that the invention has no utility, but rather that undue experimentation would be required to use the invention as claimed, especially in view of the high

degree of unpredictability in the art, the limited working examples and the scope of the claims does not commensurate with that of the objective enablement.

The high degree of unpredictability is well recognized in the monoamine reuptake art. Monoamine includes norepinephrine (NE), serotonin (5-HT), dopamine (DA), each with its subtypes of receptors and are involved in functions similar or different from one another (Schildkraut, PTO-1449). A slight modification in the structure of the compound would drastically alter its biological activity, as evidenced in the very different potencies of structurally similar substituted phenyl-tropane-carboxylic acid methyl esters (Carroll, page 2866, Table 1) and the very different Ki or IC_{50} values, as well as different selectivity for the various monoamine transporters exhibited by the structurally similar tropane analogs (Kozikowski, column 59, Table 1; Scheel-Kruger, pages 17-18, Table 1). Therefore one of ordinary skill in the art would have no basis to extrapolate the results to compounds structurally dissimilar to the examples, and expect that the variety of these structurally diverse compounds embraced by the claims would share the same biological activities. While some experimentation is permitted and every claimed embodiment need not be shown to possess the asserted activity, there should be a showing commensurate in scope with the claims. As stated in In re Cavallito 127, USPQ 202, " where the applicant seeks to obtain a monopoly in exchange for his disclosure of a group of compounds, there should be a disclosure which gives reasonable assurance that all, or substantially all of them are useful....an applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a selected few are useful and a general suggestion of a similar utility in the others". Furthermore, in the instant monoamine art, where there is a high degree of unpredictability exists, the required disclosure will be greater than for the disclosure of an invention involving a predictable factor such as a mechanical or electrical element. In re Vaeck, 20 USPQ 2d 1438.

A correlation between the binding of the compound to the monoamine transporters and the treatment of Alzheimer's disease or to all other conflicting diseases has not been fully established. It is the state of the art that there are only 4 medications (Aricept, Exelon, Reminyl and Cognex) available in the US to temporarily slow the early stages of Alzheimer's disease by inhibiting the breakdown of acetylcholine. Memantine, which blocks excess amounts of

glutamate treats late stage Alzheimer's disease.
http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.

Furthermore, the Applicant's assertion that all the structurally diverse compounds embraced by the generic claims (including the highly substituted compounds, would be effective in treating disorders or conditions caused by a deficiency in any type of monoamine concentration, including the as yet unidentified conditions/activities/disorders, any type of neurodegenerative disease etc. does not commensurate with the scope of the objective enablement.

Genetech In v. Novo Nordisk A/S (42 USPQ 2d 1001) states that 'a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion' and '[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable'

In conclusion, one of ordinary skill in the art would not be able to make and use the invention as claimed without undue experimentation except for making and using the compound wherein R1 is aryl or heteroaryl, R2 to R13 being hydrogen for treating depression.

Claim Rejections - 35 USC § 112(1)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant method of treating a disorder caused by a deficiency in monoamine concentration reaches out to as yet unidentified conditions/activities/diseases, a description of which are not found in the specification.

Conclusion

6. The compound of claims 5, 6, 31, 32, its composition, and its method for treating depression would be allowable if the 112 first written description rejection were overcome.

The closest prior art is Kozikowski (6150376) or Scheel-Kruger (WO 97/16451, PTO-1449). Kozikowski (column 13, lines 18 to 53; column 18, compounds 30, 31, 40; column 57, compounds 6.34. 6.35) or Scheel-Kruger (pages 4-5; pages 24-25, Examples 3, 4, 5) discloses a tricyclic compound derived from tropane, and the composition thereof, are described However, the prior art compound is a front-bridged or back-bridged compound whereas the instant is N-3-bridged compound.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Evelyn Huang
Primary Examiner
Art Unit 1625